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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/757,688	01/11/2001	Wolfgang Heil	PLOVIN-2A	7991

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/757,688	HEIL ET AL.	
	Examiner	Art Unit	
	Lakshmi S Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90-96,98-119,122,134 and 137-172* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *90-96,98-119,122,134 and 137-172* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-12-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment to claims, specification, remarks dated 12-3-03 and IDS dated 12-12-03 is acknowledged.

Claims 90-96, 98-119, 122, 134 and 137-152 are pending. New claims 153-172 have been added.

Claim Rejections - 35 USC § 103

Claims 90-96, 98-119,122, 134 and 137-172 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lignieres et al (hereafter Lignieres) in view of Furhmann et al (Furhmann).

Lingnieres teaches administering a combination of estrogen and micronized progesterone for postmenopausal estrogen/progestin intervention so as to protect pre- and postmenopausal women from endometrial hyperplasia (abstract, page 47, col. 1). Lingnieres suggests administering micronized progesterone for about 10 days during second half of menstrual cycle, so as to effectively prevent endometrial hyperplasia (page 51). Examiner notes that instant claims also administer drospirenone, a progestogen, in the second half of the cycle. Lingniere suggests that micronization of progesterone substantially increased the bioavailability of the hormone and oral administration of micronized progesterone has been shown to be very effective for controlling endometrial growth (page 42, col. 2). Lingniere suggests progesterone and also estradiol (page 48, col. 2), but not DSRP as claimed.

Fuhrmann teaches drospirenone a progestin that is structurally related to spironolactone but functionally having similar pharmacological profile to progesterone. Fuhrmann teaches that DSRP exhibited a high binding affinity to progesterone receptor and similar to progesterone showed a low affinity to the androgen receptors and a high affinity to mineral corticoid receptors

(page 247). Fuhrmann also suggests that DSRP exhibits an anti-androgen activity that is five to ten times higher than progesterone (page 248), which is attributed to the higher metabolic stability of DSRP as compared to that of progesterone (page 249, col. 1). It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use drospirenone of Fuhrmann in combination with estradiol for treating endometrial hyperplasia and thus protecting endometrium in postmenopausal women because Fuhrmann teaches drospirenone is a synthetic progestin that shows a similar pharmacological profile as that of natural progesterone and higher stability than progesterone. Further, while Fuhrman does not suggest micronized DSRP, Lignieres suggests micronization of progesterone for increased bioavailability upon oral administration, as high as 50% to 60%. Lignieres also suggests that while different progesterones induce different bleeding patterns, oral progesterone induces significantly less bleeding (last line of page 51). Accordingly, one of an ordinary skill in the art would have expected that DSRP of Fuhrmann that is similar in activity to progesterone also exhibit the same high efficacy in inhibiting endometrial bleeding. Further, one of an ordinary skill in the art would have expected that upon micronization of DSP the bioavailability is increased, and as a result of micronization gastrointestinal absorption is rapid, which increases the amount of surface area of the steroid that comes in to contact with the mucous membranes (paragraph connecting 53-54). Lingnieres suggests several dosing schedules for estrogen and progesterone. Accordingly, optimizing the amounts and dosages of hormones of WO, depending on the duration of administration, with an expectation to provide maximum therapeutic effect would have been obvious for one of an ordinary skill in the art. With respect to the claimed amounts of estrogen and DSRP, Lignieres suggest the effective dosages for treating endometrial hyperplasia and one

of an ordinary skill in the art would have extrapolated the dosages of progesterone to DSRP for the reasons that both progesterone and DSRP exhibit same pharmacological activity. Further, in the absence of any criticality established, choosing the particle size of DSRP by routine experimentation with an expectation achieve optimum bioavailability would have been obvious for a skilled artisan. With respect to the claimed method of treating symptoms, disorders, diseases associated with deficient endogenous levels of estrogen, Lignieres suggests endometrial hyperplasia and other postmenopausal symptoms that are within the scope of claimed symptoms, diseases etc. Further, preparing an oral pharmaceutical dosage form such as a tablet comprising estrogen, micronized DSRP and the conventional pharmacological excipients would have been within the scope of a skilled artisan because Lignieres suggests that oral administration of estrogen/progestin is effective than transdermal or intravenous.

Response to Arguments

Applicant's arguments filed 12-3-03 have been fully considered but they are not persuasive.

Applicants' arguments with respect to the rejection of claims 90-96, 98-119, 122, 134 and 138-152 as being unpatentable over Backenfeld in view of Elliesen or vice-versa are moot in view of the withdrawal of this rejection.

With respect to examiner's remarks on the declarations of Dr. Lipp and Elliesen, applicants argue that Dr. Lipp's declaration has been misread and that the declaration is not contrary to the claimed invention and instead supports instant claims. However, applicants' arguments are not persuasive because, a careful review of Dr. Lipp's declaration shows that if

examiner's argument that micronization increases the surface area and thus the exposure of DSRP to environment were to be true, then owing to its isomerization to inactive form in an acidic pH (such as stomach), such increased exposure would have been expected by one of ordinary skill in the art to expose more of the drospirenone to rapid isomerization to its inactive form in the stomach. Further, Dr. Lipp refers to the figure 1 of related application Ser. No. 09/654,227 for a comparison of the in vitro dissolution profiles for micronized (curves V1-V7) versus macrocrystalline (curve V8). Therefore, it is opined in the declaration that one of ordinary skill in the art would not have been motivated to provide orally administrable doses of drospirenone in micronized form, as recited in the application because there would be no reasonable expectation by one of ordinary skill in the art that micronization would increase its bioavailability. The teachings that some drugs can be advantageously administered in micronized form would not be considered by one of ordinary skill in the m to be applicable to all drugs, particularly not to drugs as acid sensitive as drospirenone, especially in view of its known isomerization to an inactive form under acidic conditions.

However, a careful review of the instant application, unexpected results of 5-28-02 and the figures of copending application 09/654,227 shows that none of the formulation recite the actual micron sizes of DSRP, which is relevant to its dissolution as evident from the results. Further, it is clear from the data that even micronized DSRP undergoes isomerization to inactive form and hence applicants' argument that the unexpected finding that micronization of DSRP improves bioavailability is not persuasive. Besides, the higher dissolution profiles observed with the micronized form of DSRP are consistent with examiner's position that upon micronization that surface area increases and thus an increase in the bioavailability (measures as dissolution),

as also stated in the instant application. On page 7, lines 15+ it is stated " Drospirenone, which may be prepared substantially as described in, e.g., US 4,129,564 or 15 WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various PH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the compound, it is therefore advantageously provided in a form that promotes rapid dissolution thereof". Therefore, it is examiner's position that the observed increase in the dissolution of DSRP upon micronization and hence bioavailability is not unexpected and would have been obvious for one of an ordinary skill in the art at the time of the instant invention.

Conclusion

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 12-12-03 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lakshmi S Channavajjala
Examiner
Art Unit 1615

March 30, 2004

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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